Pharmacological reversal of synaptic and network pathology in human MECP2-KO neurons and cortical organoids.

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Public Summary:
In this publication, we develop a novel platform to screen drugs for conditions caused by mutations in the MECP2 gene, such as Rett syndrome. We use traditional 2D cultures and an innovative 3D platform to test drugs to correct a series of molecular, cellular and electrophysiological readouts in stem cell-derived neurons. We found two promising candidates that were also tested in human brain organoids. One of the candidate repurposed drug, Nefiracetam, is now moving to clinical trials.

Scientific Abstract:
Duplication or deficiency of the X-linked MECP2 gene reliably produces profound neurodevelopmental impairment. MECP2 mutations are almost universally responsible for Rett syndrome (RTT), and particular mutations and cellular mosaicism of MECP2 may underlie the spectrum of RTT symptomatic severity. No clinically approved treatments for RTT are currently available, but human pluripotent stem cell technology offers a platform to identify neuropathology and test candidate therapeutics. Using a strategic series of increasingly complex human stem cell-derived technologies, including human neurons, MECP2-mosaic neurospheres to model RTT female brain mosaicism, and cortical organoids, we identified synaptic dysregulation downstream from knockout of MECP2 and screened select pharmacological compounds for their ability to treat this dysfunction. Two lead compounds, Nefiracetam and PHA 543613, specifically reversed MECP2-knockout cytologic neuropathology. The capacity of these compounds to reverse neuropathologic phenotypes and networks in human models supports clinical studies for neurodevelopmental disorders in which MeCP2 deficiency is the predominant etiology.